# FINAL SYNOPSIS OF THE Ph.D. THESIS TO BE SUBMITTED TO DEPARTMENT OF CHEMISTRY MANGALORE UNIVERSITY

## FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY

**TITLE OF THE THESIS:** **SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL STUDIES OF SOME NOVEL NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS**


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# SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL STUDIES OF SOME NOVEL NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

## SYNOPSIS

# CHAPTER-1

## A BRIEF REVIEW ON CHEMISTRY OF HETEROCYCLES AND NITROGEN-CONTAINING HETEROCYCLES

### 1. INTRODUCTION

According to the Collins English Dictionary, a heterocyclic compound is defined, as an organic compound containing a closed ring of atoms, at least one of which is not a carbon atom. Therefore, heterocyclic compounds can be defined as organic cyclic compounds which contain at least one atom other than carbon, like sulfur, oxygen, or nitrogen as hetero atom in their ring structure. These compounds are essential to the biological system due to the distinctive nature of the skeletons they possess. They are naturally present in extremely high concentrations in macromolecules, vitamins, drugs, hormones, etc.

Synthetically produced heterocycles are used as agrochemicals, and pharmaceuticals and perform a significant role in living things and new drug design.[1, 2] Heterocycles demonstrated a wide range of biological activity, as illustrated in the diagram below.[3–10]

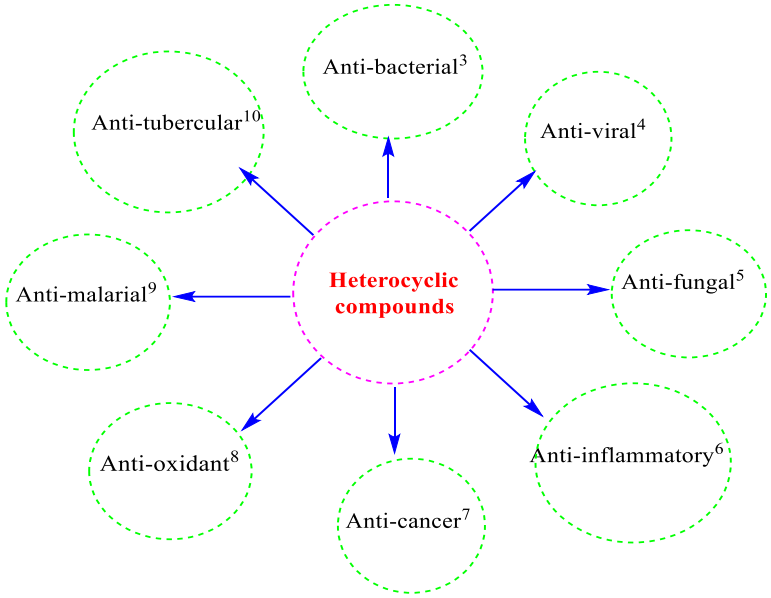
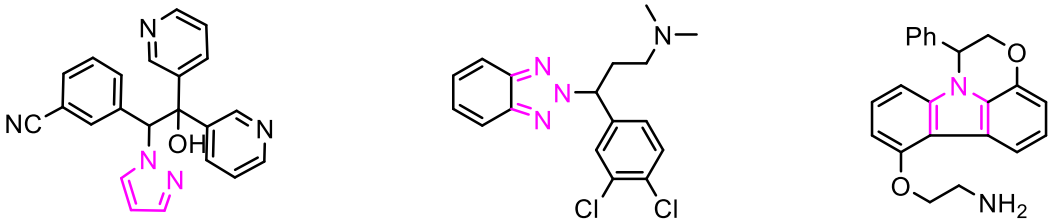



**Figure 1** Biological activity of heterocyclic compounds

Nitrogen-containing heterocyclic compounds are important heterocycles that have contributed significantly to medicinal chemistry. Five-membered nitrogen heterocycles having N-alkyl derivatives are crucial building blocks and form structural units of many biologically active molecules (**Fig. 2**).[11-13] Pyrazoles (**1**) may be used to treat arrhythmia, and benzotriazole (**2**) may have antibacterial activity. Carbazole (**3**) is equally capable of acting as a serotonin receptor modulator and can be used in the treatment of depression, anxiety, and other mental disorders.




**1** **2** **3**

**Figure 2** Examples of biologically active compounds that contain fragments of five-membered N-alkylated heterocycles

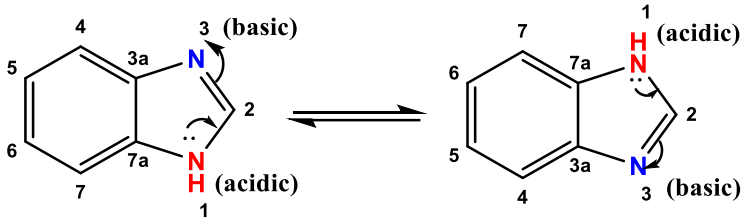
Keeping in view of the diverse biological and pharmacological activities of nitrogen-containing five- and six-membered ring heterocyclic compounds, efforts have been made to synthesize a new series of five or six-membered heterocycles bearing nitrogen atoms and to screen them for biological activities. The strategies employed in such synthetic studies, as well as the results, are discussed in this thesis.

# CHAPTER-2

# SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL HYDRAZONES CARRYING BENZIMIDAZOLE AND PYRENE/VANILLIN MOIETY

## 2.1 INTRODUCTION

Benzimidazoles are a class of five-membered heterocycles with two heteroatoms wherein an imidazole ring is fused to a benzene ring.[14, 15] The addition of a heterocyclic ring system to benzimidazole improves its pharmacological properties. **Figure 3** illustrates the two isomeric forms of benzimidazole and their method of numbering. N-Ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$, is the most popular benzimidazole compound in nature.[16].




**(1)**

**Figure 3** Tautomeric forms of benzimidazole.

Simply heating the o-phenylenediamine and formic acid together affects the benzimidazole moiety. The synthesis of benzimidazoles has been developed by reacting o-phenylenediamine with aldehydes in aqueous media using boric acid as an efficient catalyst under mild reaction conditions. Benzimidazole was synthesized by reacting o-phenylenediamine with carboxylic acids or their derivatives (nitriles, amides, esters, chlorides)[17-19] and aldehydes or alcohol, according to several researchers,[19,20] in various solvents such as $CH_3CN$, MeOH, $CHCl_3$, ether, and DMF. Similarly, it can be prepared from 4-chloro-3-nitrobenzoic acid by nitro reductive cyclization in DMSO

solvent. **Figure 4** depicts some commercially available active anthelmintic drugs from the benzimidazole class, such as albendazole **(2)**, mebendazole **(3)**, triclabendazole **(4)**, and others.

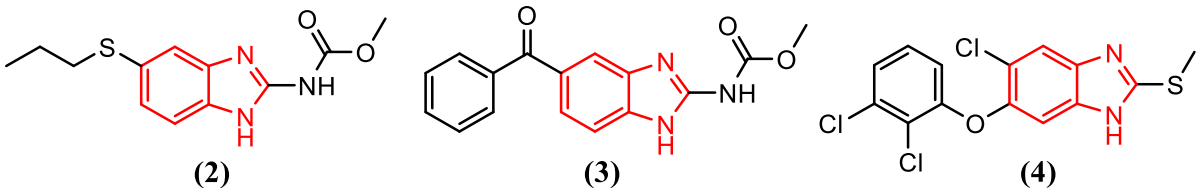
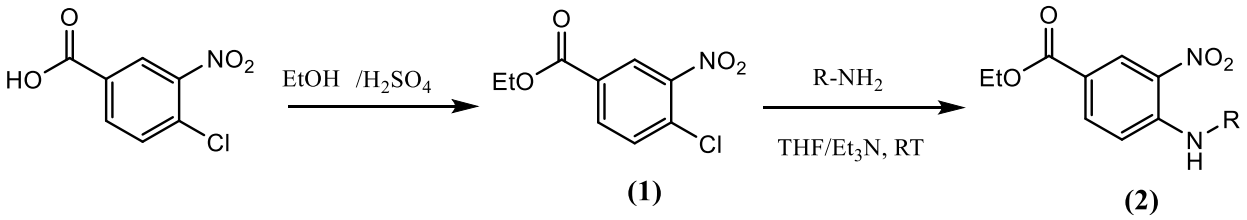
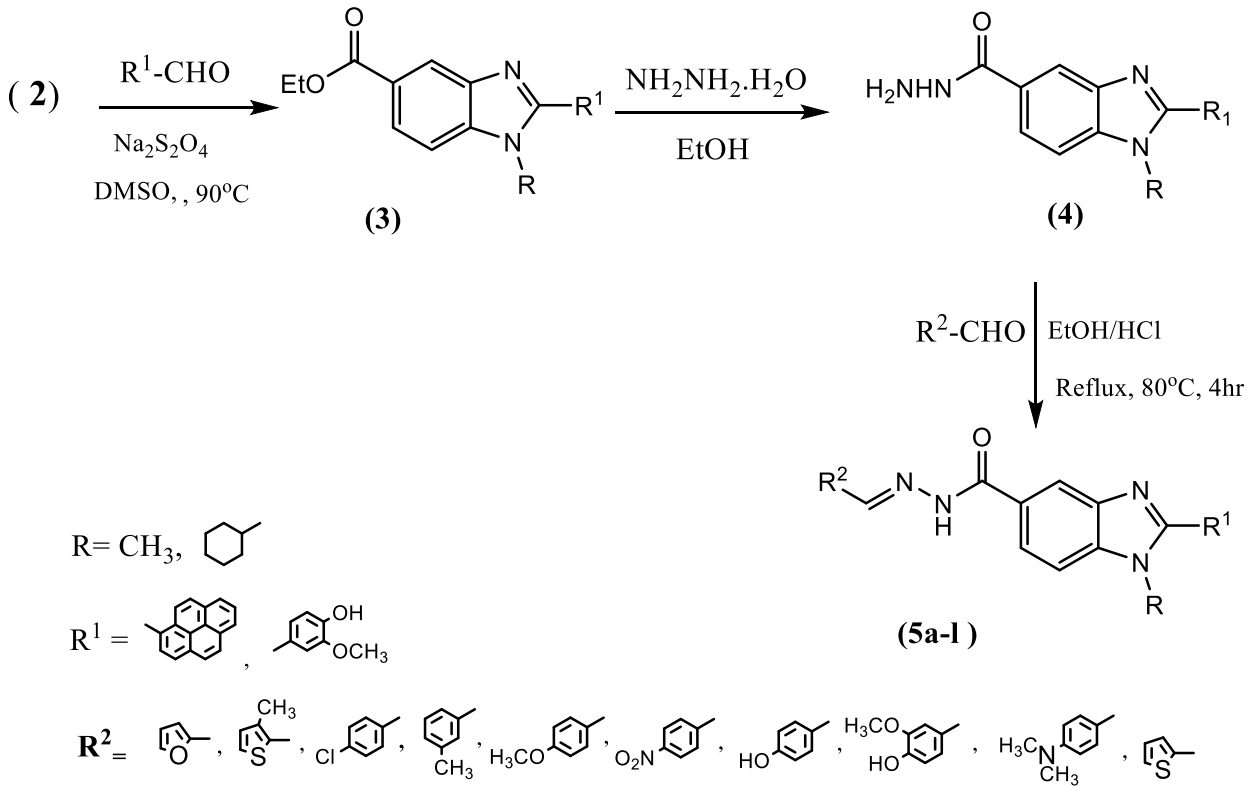



**Figure 4.** Benzimidazole-based drugs.

## 2.2 MATERIALS AND METHODS

The final compounds (**5a-l**) were synthesized using adaptable and efficient synthetic methods described in **Scheme-1**. The esterification of 4-chloro-3-nitrobenzoic acid with ethanol yielded a compound (**1**). The amino derivatives (**2**) were obtained in 70-95 % yields by treating compounds (**1**) with appropriate aniline in tetrahydrofuran in the presence of triethylamine as a catalyst at room temperature. The reaction of compounds (**2**) with different aldehydes by one-pot nitro reductive cyclization using sodium dithionite in DMSO yielded compounds (**3**), and the reaction of compounds (**3**) with hydrazine hydrate in ethanol yielded carbohydrazide bearing benzimidazole derivatives (**4**). Finally, hydrazones carrying benzimidazole moiety (**5a-l**) were synthesized by condensation of hydrazide (**4**) with various substituted aldehydes in ethanol and a few drops of hydrochloric acid (**Scheme-1**).






**Scheme-1: Synthetic route of final compounds (5a-l)**

TLC, Merck Silica Gel 60 F–254 thin layer plates, was used to monitor the progress of the reaction. Melting points have been measured on an open capillary tube in an Innovative DTC-967A digital melting point apparatus and are uncorrected. All the synthesized compounds were characterized by IR, $^{1}$H-NMR, and Mass spectral data.

## 2.3 PHARMACOLOGICAL STUDIES

### 2.3.1 Antimicrobial Evaluation

The newly synthesized compounds have been evaluated for their in vitro antibacterial activity against (*S. mutans* & *S. aureus*) Gram-positive bacteria, (*P aeruginosa & E. coli*) Gram-negative bacteria, and antifungal activity against *A. niger* and *C. albicans* by the disc diffusion method.[21] The results obtained, indicated that the synthesized final compounds exhibited moderate to good antibacterial and antifungal activity against all bacterial and fungal strains. However, all the synthesized compounds showed better antifungal activity than antibacterial activity

### 2.3.2 Antioxidant Activity

Antioxidants are substances that may guard cells against the harm brought on by unstable molecules called as free radicals. The DPPH test is a quick and accurate method for determining radical scavenging action because it is focused on the ability of DPPH, a stable free radical, to decolorize in the presence of antioxidants. The test compounds' free radical scavenging activity was measured using stable DPPH as a control, and the results were compared to the standard antioxidant Butylated Hydroxy Anisole, abbreviated as BHA.[22]

$$\textbf{Free radical scavenging activity (\%)} = \frac{A_c - A_s}{A_c} \times 100$$

Where $A_c$ is the absorbance of the control reading and $A_s$ is the absorbance of the test samples.
The biological activity results revealed that some of the synthesized compounds had moderate to good antioxidant activity.

# CHAPTER-3

# DESIGN, SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL 1,3,4-OXADIAZOLE-2-THIOL AND THEIR S-DERIVATIVES

## 3.1 INTRODUCTIONS

Oxadiazole is a member of the azole class of heterocyclic aromatic compounds having a parent compound with molecular formula $C_2H_2N_2O$ and consisting of one oxygen and two nitrogen atoms. Depending on the placement of the nitrogen in the ring, they have four isomeric forms such as 1,2,3-; 1,2,4-; 1,2,5-; and 1,3,4-oxadiazole. Except for the 1,2,3-isomer which is unstable and returns to the diazoketone tautomer, the other oxadiazole isomers are stable and found in variety of chemotherapeutic and antibiotic agents. 1,3,4-Oxadiazole is resulted from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogen (-N=).[23] Oxadiazoles can be found in four different isomeric structures (**Fig. 5**).

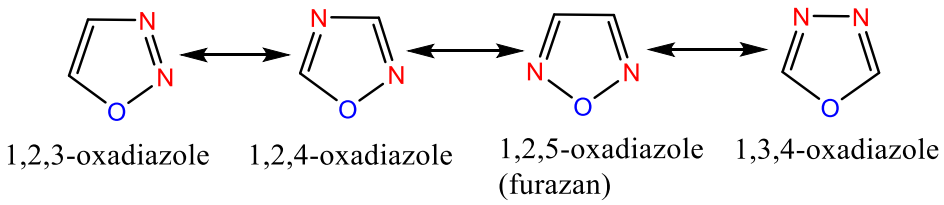
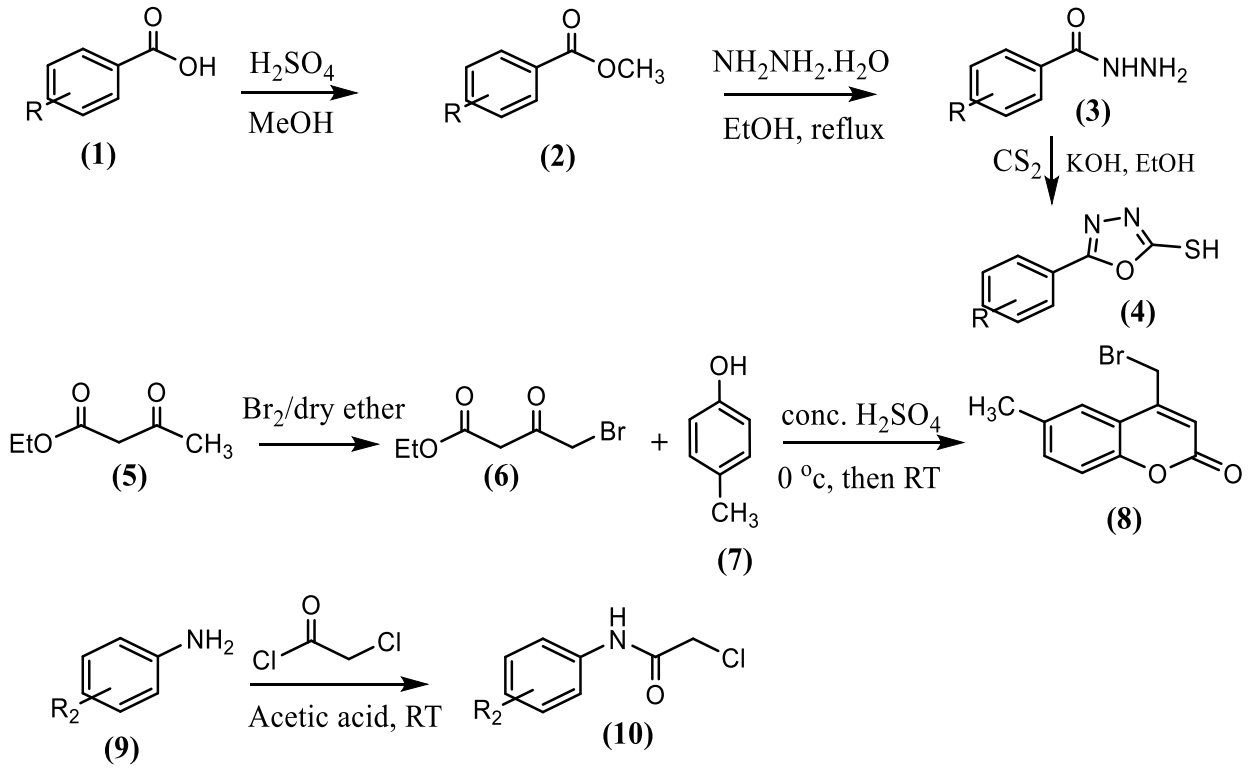


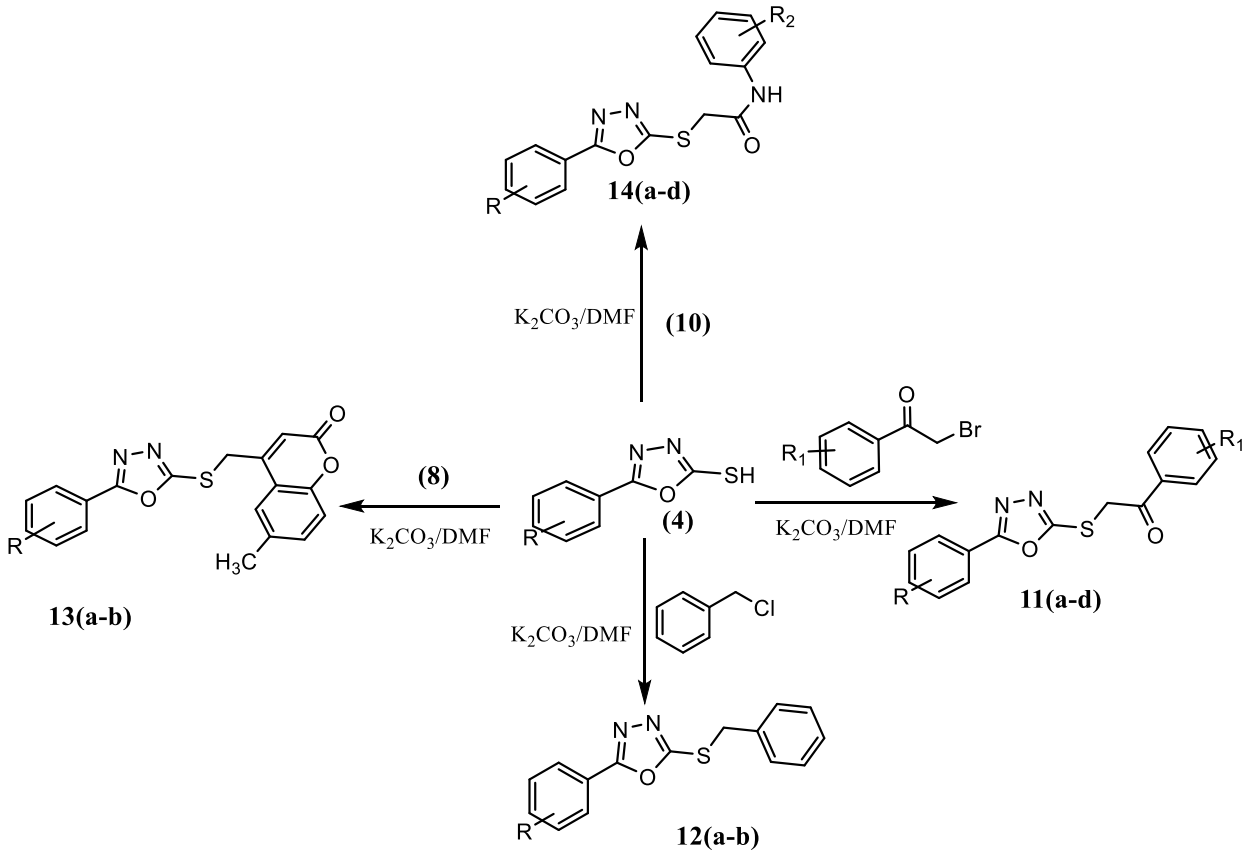

**Figure 5:** Four Isomeric Forms of Oxadiazoles

Various oxadiazole derivatives exhibit varied pharmacological activity. The activity is enhanced by the attachment of a heterocyclic ring system to the parent oxadiazoles. Oxadiazole derivatives such as raltegravir[24], fenadiazole[25], zibotentan[26], ataluren[27], and tiodazos[28] are successfully used as an HIV drug, a hypnotic drug, and anticancer activity of the specific Endothelin Receptor Antagonists, a nonsense mutation Duchenne muscular dystrophy (nmDMD) treatment and benign prostatic hyperplasia (BPH), hypertension and post-traumatic stress disorder treatment in clinical practices respectively.

### 3.2 Materials and Methods

The reaction sequences followed for the synthesis of the final compounds are outlined in **Scheme 2**. The different 4-substituted methyl benzoates **(2)** are prepared from its acid derivatives using the standard esterification method[29]. 4-Substituted benzoyl hydrazine **(3)** was synthesized in good yield from the reaction of ester **(2)** with an excess of hydrazine hydrate in ethanol. Intramolecular cyclization of acid hydrazide **(3)** with carbon disulfide in ethanolic KOH resulted in the formation of 5-(4- substituted phenyl)-1,3,4-oxadiazole-2-thiol **(4),** which was then S-alkylated by reacting with suitably substituted phenacyl bromides, benzyl chloride, 4-(bromomethyl)-6-methyl-2H-chromen-2-one and substituted 2-chloro-N-phenylacetamide to give compounds 5-(4- substituted phenyl)-1,3,4-oxadiazole-2-thiol **11(a-d)**, **12(a-b)**, **13(a-b)**, and **14(a-d)** in good yield. The completion of the reaction was monitored by TLC using silica gel as stationary phase and ethyl acetate – petroleum ether as mobile phase.






R=$CH_3$, $OCH_3$, Cl; $R_1$=$CH_3$, $OCH_3$ and $R_2$=$NO_2$, Cl

**Scheme-2:** General synthetic route for compounds **11(a-d), 12(a-b), 13(a-b) & 14(a-d).**

The melting points were measured in open capillaries on EQ 730 EQUIPTRONICS digital melting point apparatus and are not corrected. Thin-layer chromatography was carried on pre-coated silica gel plates (silica gel 0.25 mm, 60G F254). A Vario-EL (Elementar-III) model was used for the CHN analysis. All synthesized derivatives were characterized by spectroscopic analysis (IR, $^{1}$H-NMR, $^{13}$C-NMR, and mass).

## 3.3 PHARMALOGICAL STUDIES

### 3.3.1 Antioxidant activity

DPPH (2,2-diphenyl-1-picrylhydrazyl) was used for the study. Free radical scavenging activity of compounds was measured by DPPH as per the reported procedures[22] Butylated hydroxyanisole (BHA) was used as standard. The DPPH free radical scavenging was calculated according to the following equation:

DPPH scavenging activity (%) $= \frac{(Ac - As)}{Ac} x\ 100$

Where $A_c$ is the absorbance of the control reading and $A_s$ is the absorbance of the test samples. According to the antioxidant activity results, the majority of the synthesized compounds showed moderate activity.

### 3.3.2 Cytotoxicity assay

Four compounds were tested for cytotoxicity in the MTT assay. The human lung cancer (A549) cells were provided by Yenepoya Research Centre, Mangalore, India, and used for the study. The test method followed is based on the standard protocol[30]. Results have been expressed in the form of $IC_{50}$ (half-maximal Inhibitory Concentration) value.

Human lung cancer (A549) cells were used for the study. They were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FBS and 1% antibiotic-antimycotic solution. Cells were maintained at 37°C and 5% $CO_2$ in a humidified atmosphere throughout the experiments.

Cytotoxicity of the test compounds was assessed using Methyl Thiazolyl Tetrazolium (MTT) assay (Mossman, 1983). At a seeding density of 5000 cells/well, cells were seeded onto 96 well microtiter plates. After adherence, they were treated with different concentrations of the test compound (solubilized in DMSO) viz., 6.25, 12.5, 25, 50, 100, and 200 ug/ml. After 24 and 72 hrs. of incubation with test compounds, MTT

reagent was added to the wells and incubated at 37°C for 4 hrs. Formazan crystals formed were solubilized using DMSO and absorbance was recorded at 570 nm using a multimode microplate reader (F1uoSTAR Omega, BMG Labtech). Percentage cytotoxicity of the test compound was calculated with respect to untreated cell control[31].

$$\text{Percentage of inhibition (\%)} = \frac{\text{OD control} - \text{OD sample x } 100\%}{OD\ control}$$

The average of three replicates was then obtained. Every test agent's cytotoxicity is measured in $IC_{50}$ value.

The MTT assay analysis of human lung cancer revealed that the synthesized compounds had good in vitro anticancer activity and a low $IC_{50}$ value. GraphPad software version-5 was used to tabulate and plot the graph.

# CHAPTER-4

# SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NOVEL 1, 2, 3-TRIAZOLE DERIVATIVES

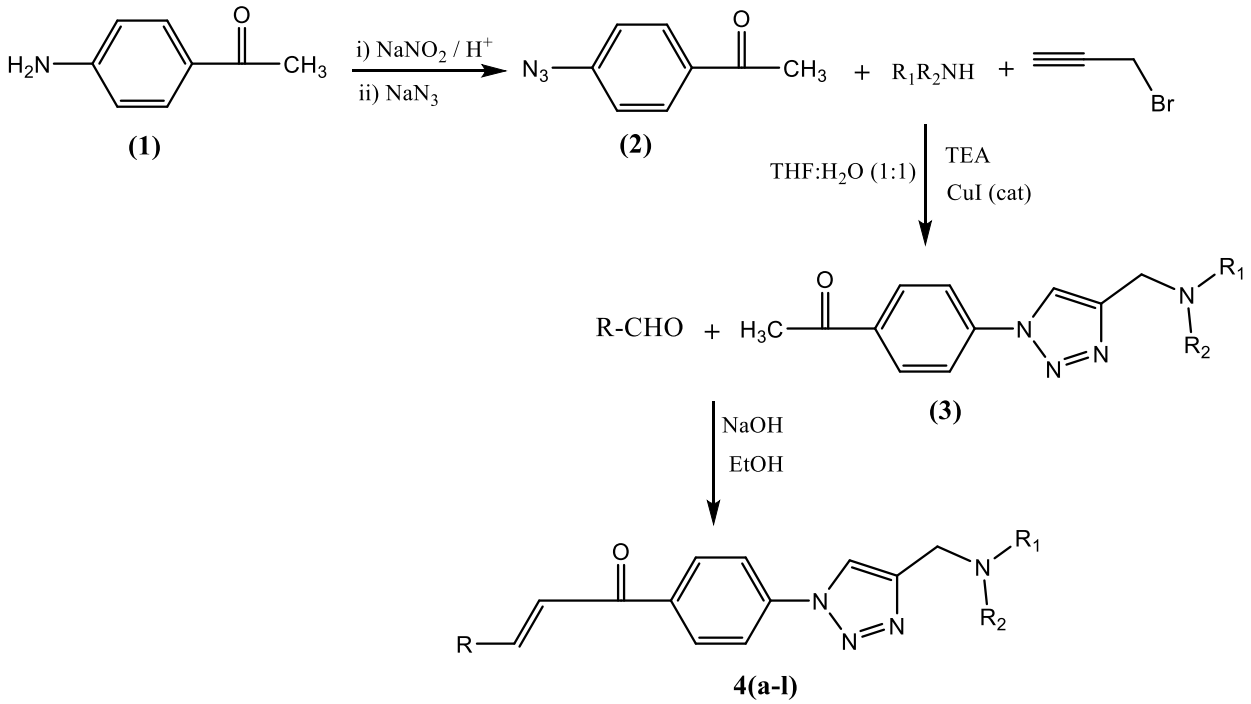
## 4.1 INTRODUCTION

1,2,3-triazole is one of the types of triazoles with the molecular formula $C_2H_3N_3$ and a five-membered ring having two carbon atoms and three nitrogen atoms.[32] The azide-alkyne Huisgen cycloaddition, in which an azide and an alkyne undergo a 1,3-dipolar cycloaddition reaction, can be used to produce substituted 1,2,3-triazoles. 1,2,3-Triazole is used as a bioisostere in medicinal chemistry[33] as a building block for more complex chemical compounds, such as prescription drugs like mubritinib and tazobactam. Advances in click chemistry (the copper-catalyzed azide-alkyne cycloaddition [Cu-AAC] reaction), as well as various synthetic methodologies for 1,2,3-triazole scaffolds (e.g., derivatives, hybrids, and conjugates), have been used in medicinal chemistry.[34] The 1,2,3-triazole nucleus is associated with variety of activities such as anticancer,[35,36] antimicrobial,[37-39] anti-infective,[40,41] and antioxidant[42,43] etc. Furthermore, triazole-linked derivatives were widely used in peptides to imitate a trans-amide bond and were found to influence adenosine diphosphate ribosylation biology, [44] despite their danger to native peptide activity.[45]

### 4.2. MATERIALS AND METHODS

Condensation of 1,2,3-triazole carrying ketones (**3**) with various substituted aldehydes in the presence of alkali yielded the chalcone linked to 1,2,3-triazoles **(4a-l**). The 1,2,3-triazole ketones (**3**) were synthesized in our laboratory by a one-pot reaction of azide ketones (**2**), propargyl bromide, and secondary amines in alkaline media employing copper iodide as a catalyst and a mixture of THF and water as solvent. The azido ketone (**2**) was prepared by diazotization of p-amino acetophenone **(1)** with sodium azide. **Scheme-3.**

**Reaction scheme**




**Where R**= p-Chlorophenyl, p-Methylphenyl, p- Methoxyphenyl, 5-Methylfuranyl, and

-N**$R_1R_2$**= Morpholino, ethyl piperazine, methyl piperazine, piperidine

**Scheme-3** Synthetic scheme for final synthesized compounds **4(a-l)**

The structures of the newly synthesized compounds are established by spectral and analytical data.

## 4.3 PHARMACOLOGICAL STUDIES

### 4.3.1. Antioxidant Activity

The antioxidant activity of the newly synthesized compounds **4(a-l)** was tested using the DPPH scavenging assay. The percentage activity was compared to the activity of the standard drug (Butylated hydroxyanisole), which was assumed to be 100%, and the results revealed that the new compounds had moderate antioxidant activity.

### 4.3.2 Antimicrobial Activity

The newly synthesized compounds **4(a-l)** were tested in-vitro for antimicrobial activity, and the results showed that they had moderate antimicrobial activity.

# CHAPTER-5

# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF SOME NOVEL TRIAZOLOTHIADIAZOLES

## 5.1 INTRODUCTION

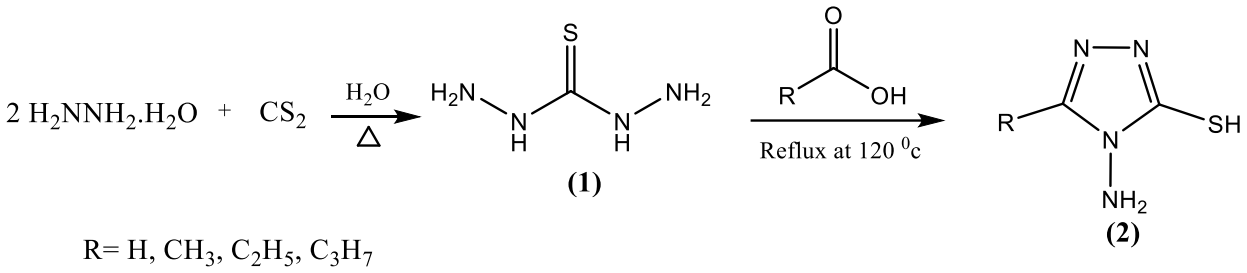
The covalent conjugation of biologically active moieties, acting through various mechanisms to produce a compound with improved activity and reduced toxicity, is one of the most fundamental concepts in drug design. The fused ring of triazoles and thiadiazoles called triazolothiadiazoles signifies a vital class of nitrogen frontline heterocyclic compounds which possess a broad spectrum of pharmacological activity such as antifungal,[46] antibacterial,[46,47] anticancer,[48] cytotoxic,[49] anthelmintic,[50] antitubercular,[51] anti-inflammatory,[52] and antidepressant.[53] Based on this concept and the pharmacological activities demonstrated by various 1,2,4-triazole and 1,3,4-thiadiazole derivatives, our research aims to combine the structure of four secondary amines containing aromatic acids with 1,2,4-triazoles to yield fused triazolothiadiazole derivative products using a traditional synthetic strategy.

## 5.2 MATERIALS AND METHODS

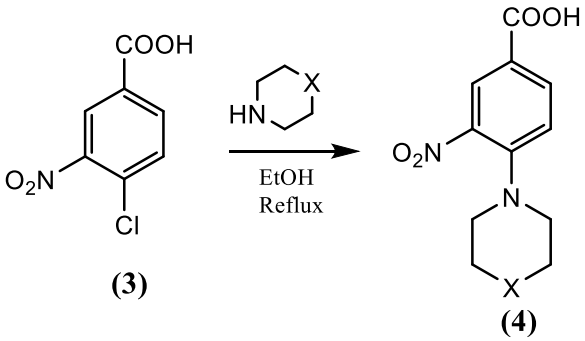
The synthesis of hitherto unreported title compounds **5**(**a-l**) is outlined in (**Scheme 4.3**). The starting material thiocarbohydrazide (**1**) was prepared by reacting hydrazine hydrate with carbon disulfide.[54] It was then refluxed with various carboxylic acid derivatives (formic, acetic, propionic, and butyric acids) to yield 5-substituted-4-amino-3-mercapto-1,2,4-triazole derivatives (**2**)[55] (**Scheme 4.1**).

The starting material required namely substituted 4-(morpholino/methylpiperazin-1-yl/piperidin-1-y)-3-nitrobenzoic acids (**4**) were synthesized by refluxing 4-chloro-3-nitrobenzoic acid (**3**) in ethanol with various secondary amines (**Scheme 4.2**.).

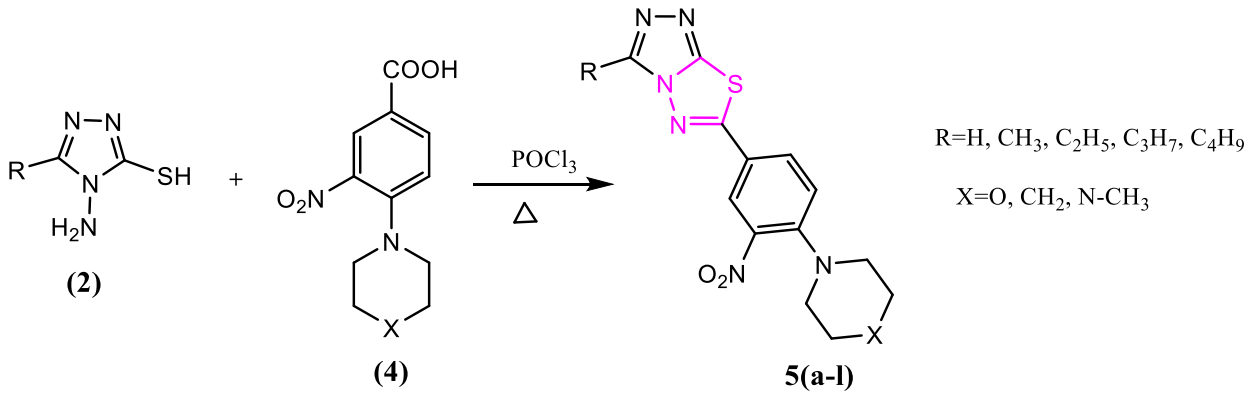
The final compounds (1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles carrying 4-substituted secondary amine) (**5**) were obtained by condensing compounds (**2**) with 4-(substituted secondary amino)-3-nitrobenzoic acids (**4**) in phosphorus oxychloride (**Scheme 4.3**).




**Scheme 4.1**




**Scheme 4.2**




**Scheme 4.3**

The completion of the reaction and the purity of the compounds were monitored by TLC using silica gel plates (Merck) with hexane: ethylacetate (2:8) as the mobile phase. The chemical structures of the newly synthesized compounds have been confirmed by recording their IR, $^{1}$H-NMR, mass and elemental analysis.

## 5.3 PHARMACOLOGICAL STUDIES

### 5.3.1 Antioxidant activity

The antioxidant activity of the newly synthesized compounds **5(a-l)** was determined using the DPPH free radical scavenging assay. The DPPH free radical scavenging was calculated according to the following equation:

$$\text{DPPH scavenging activity (\%)} = \frac{(Ac - As)}{Ac} \boldsymbol{x}\ \mathbf{100}$$

Where, $A_c$ is absorbance of the control reading and $A_s$ is absorbance of the test samples.

### 5.3.2 Antimicrobial activity

The antimicrobial activity of the newly synthesized Triazolothiadiazole were screened against four bacterial and two fungal strains employing the cup-plate method. Ampicillin and Bavistin were used as the standards for bacterial and fungal activities, respectively. The antimicrobial assay results revealed that the tested compounds had moderate antibacterial and antifungal activity when compared to the standard drugs.

# CHAPTER-6

# SYNTHESIS OF NOVEL HYBRID PYRAZOLINES INCORPORATED WITH THIAZOLE AND PYRAZOLE NUCLEUS

## 6.1 INTRODUCTION

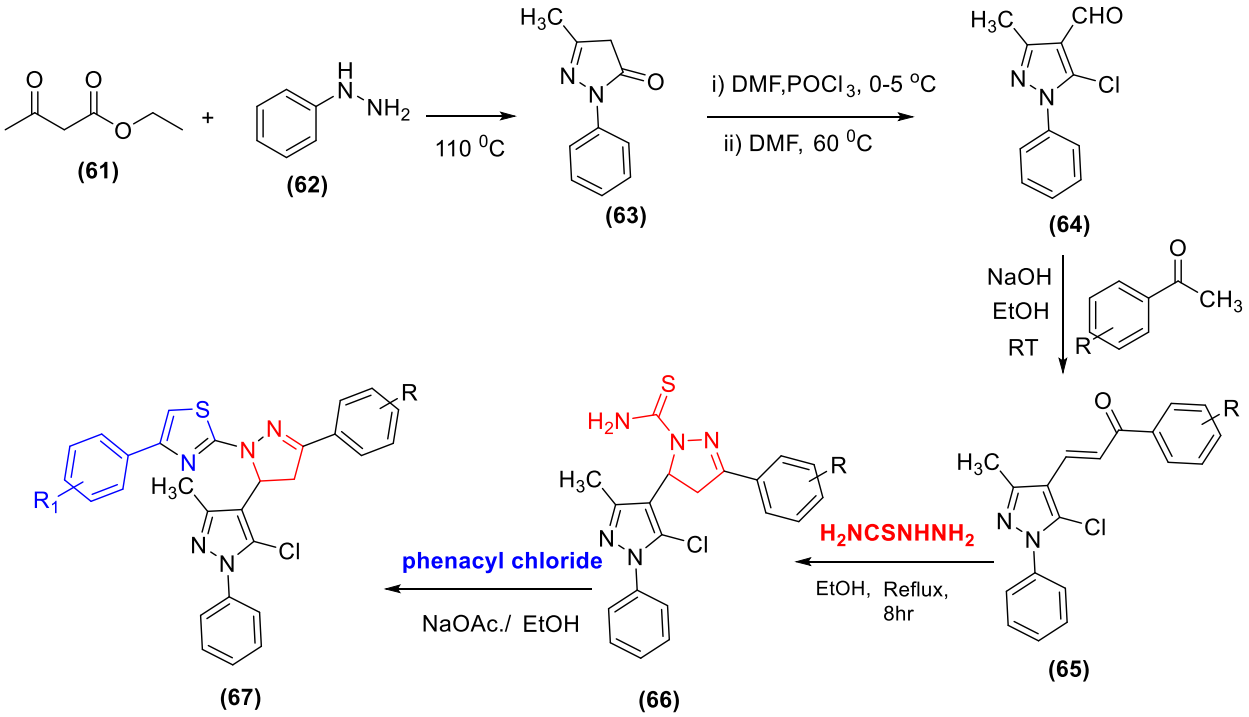
Pyrazole's nucleus is a well-known example of aromatic heterocycles containing two adjacent nitrogen and three carbon atoms in their ring structure. In recent years, the synthesis of a new class of compounds containing the thiazole and pyrazole moieties in a single entity may result in increased biological activity due to the synergistic effect of the two rings. Pairs of pyrazole and thiazolyl have shown antitubercular,[56,57] antimycobacterial activities,[58] anti-inflammatory, antimicrobial,[59] anticancer,[60,61] and FabH inhibitors.[62] Some pyrazole and thiazole moiety drugs that are currently on the market include sildenafil (to treat erectile dysfunction and pulmonary arterial hypertension), celecoxib (a COX-2 inhibitor and a nonsteroidal anti-inflammatory drug), rimonabant (an anorectic anti-obesity drug), and fomepizole (to treat methanol and ethylene glycol poisoning) with pyrazole moiety; and abafungin (antifungal agent), sulfathiazole (antimicrobial), tiazofurin (chronic myeloid leukemia (CML) drug) and Ritonavir (antiretroviral) with a thiazole moiety.

## 6.2 MATERIALS AND METHODS

A series of novel 5-chloro-4-(1-(4-(substituted phenyl) thiazol-2-yl)-4,5-dihydro-3-(substituted phenyl)-1H-pyrazol-5-yl)-4,5-dihydro-3-methyl-1-phenyl-1H-pyrazole derivatives **(67)** were synthesized by a five-step reaction sequence as shown in **scheme-5.**

To begin, ethyl acetoacetate (**61**) was heated with phenylhydrazine (**62**), yielding 3-methyl-1-phenyl-1H-pyrazol-5-one (**63**), which was then subjected to Vilsmier Hack Formulyation (DMF, $POCl_3$ at 0-5 $^oC$ and further refluxed at 60 $^oC$), yielding 5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-carboxaldehyde (**64**). It was then dissolved in alcoholic sodium hydroxide solution and stirred at room temperature with various substituted acetophenones to yield 3-(5-chloro-3-methyl-1-

phenyl-1H-pyrazol-4-yl)-1-(substituted aryl) prop-2-ene-1-one derivatives (**65**). 3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(substituted aryl) prop-2-ene-1-one **(65)** which was then reacted with thiosemicarbazide gave 5-(5-chloro-4,5-dihydro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-3-(substituted phenyl)pyrazole-1-carbothioamide (**66**). The later one was then treated with phenacyl bromide or chloride, in alcohol medium and stirred at room temperature, to give the 5-chloro-4-(1-(4-(substituted phenyl)thiazol-2-yl)-4,5-dihydro-3-(substituted phenyl)-1H-pyrazol-5-yl)-4,5-dihydro-3-methyl-1-phenyl-1H-pyrazole (**67**) in good yields (72–96%)




**Scheme-5:** Synthetic rout of the novel synthesized compounds

The melting points of the prepared compounds were determined on the EQ 730 EQUIPTRONICS digital melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8000 spectrophotometer using KBr disk. The $^{1}$H-NMR. Chemical shifts were reported in ppm (δ) units relative to TMS (ppm) and coupling constants (J) in Hz units. The mass spectra of the synthesized compounds were recorded at 70 eV using a Shimadzu LC-MS-8030 mass spectrometer.

## 6.3 PHARMACOLOGICAL STUDIES

### 6.3.1. Antioxidant Activity

The antioxidant activity of the newly synthesized compounds **66(a-j**) and **67(a-c**) was determined using the DPPH free radical scavenging assay and all the new compounds showed significant antioxidant activity.

## 6. REFERENCES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## List of Publications

### A. Journals

1. Synthesis, characterization and biological studies of novel series of triazolyl Schiff bases bearing thiazole moiety and their S-derivatives

   Jean Baptiste Nkurunziza, Balakrishna Kalluraya and **Desta Gebretekle;** *Journal of Applicable Chemistry* 2020, 9 (4): 556-565
2. Synthesis and Biological Evaluation of Some Novel Hydrazones Carrying Benzimidazole and Pyrene/Vanillin Moiety

   **Desta Gebretekle**, Balakrishna Kalluraya and N. Manju; *Journal of Applicable Chemistry* 2021, 10 (1): 12-2

### B. Conference Proceedings

1. Synthesis and pharmacological studies of novel triazole-linked pyrazoline hybrid compounds

   **Desta Gebretekle** and Balakrishna Kalluraya presented at 35$^{th}$ Annual conference Indian council of chemists 22$^{nd}$-24$^{th}$ December, 2016, Haribhai V. Desai College, Pune in association with College of Engineering, Pune (poster no. OP-17)
2. Synthesis and biological evaluation of some novel hydrazones carrying benzimidazole and pyrene moiety

   **Desta Gebretekle**, Balakrishna Kalluraya and N. Manju at 36$^{th}$ Annual conference Indian council of chemists 26$^{th}$-28$^{th}$ December, 2017, School of Chemistry, Andhra university, Visakhapatnam-53003 (A.P.) (Oral presentation number, OO-05)
3. Synthesis of novel pyrazoles hybrid pyrazolines incorporated with thiazole and pyrazole nucleus

   **Desta Gebretekle** and Balakrishna Kalluraya at 37$^{th}$ Annual conference Indian council of Chemists 12$_{th}$-14$^{th}$ December, 2018, national Institute of Technology Karnataka (NITK) Surathkal, Mangalore-575025 (Karnataka), (Oral presentation number, OO-05)

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| **Desta Gebretekle** | **Prof. Balakrishna Kalluraya** |
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